REMARKS

The foregoing amendments: (i) cancel duplicative claim 56; (ii) present three (3) additional claims for consideration; and (iii) correct typographical errors in the specification and claims. Applicant also encloses marked-up copies of the amended paragraphs within the specification and the amended claims as Appendix A and Appendix B, respectively. No new matter has been added, for example, naturally occurring porphyrins are referenced on page 9, lines 15-19 and page 16, lines 7-14, treatment times under forty-eight hours are referenced on page 10, lines 17-18, page 11, lines 1-2, page 12, lines 1-4, and page 12, lines 5-8, and the object of the treatment is noted on page 1, lines 15-24. Entry of these amendments is respectfully requested. A check in the amount of Twenty-Seven Dollars ($27.00) is enclosed (to cover the cost of three additional claims). If this is incorrect, or if any additional fees are required, please charge (or credit any overpayment) to Deposit Account No. 02-4467.

RESPONSE TO OFFICE ACTION

In the Office Action mailed September 4, 2002, the Examiner rejected claims 1-57 under 35 U.S.C. § 103(a) as being unpatentable over Robinson et al. (U.S. Patent No. 6,054,449), Lamuraglia (WO 01/24825 A2) or Allison (WO 01/35997 A2).

Applicant respectfully submits that the Robinson et al and Lamuraglia references do not teach or suggest all the limitations of Claims 1-57. Furthermore, based on the teachings of Robinson or Lamuraglia, one skilled in the art would neither consider utilizing short wavelengths of light to excite a photosensitizer drug, nor appreciate the benefits of using short wavelengths of light for this purpose. With respect to the Allison reference, Applicant submits herewith a declaration under 37 CFR § 131 to address the Examining Attorney's concerns. (Exh. A).

I. Overview of the Claimed Invention.

The present invention relates to a method in which photodynamic therapy (PDT) is employed by utilizing wavelengths of light within the range of about 390 to about 610 nm to excite photosensitizer drugs for treatment of cardiovascular occlusions. Through the use of such shorter wavelengths, the unexpected results of improved safety (reduction of surrounding tissue damage) and efficacy are achieved.

II. Robinson Does Not Teach the Claimed Invention.

The Examiner has rejected claims 1-57 (claim 56 has been cancelled) under 35 U.S.C. § 103(a) as being unpatentable over Robinson et al. (U.S. Patent No. 6,054,449). Robinson generally describes a method of PDT treatment using a psoralen bound to a photosensitizer drug, delivery of UV or short wavelength light to the break apart the psoralen-photosensitizer drug compound, then the delivery of a long wavelength light (greater than 610 nm) to the photosensitizer. There is no statement or suggestion of the use of short wavelengths of light to excite the photosensitizer.

Claim 1, as well as the claims dependent on claim 1, are directed to a method of PDT treatment using photoactivating light wavelengths in the 390 to 610 nm range to activate the photosensitizer drug. Claim 57 recites a method of PDT treatment using photoactivating light wavelengths in the 440 to 610 nm range to activate the photosensitizer drug.

While Robinson arguably discloses the use of UV or short wavelengths of light, the light at these wavelengths is delivered to break apart the psoralen-photosensitizer drug compound, not to activate the photosensitizer. (See Robinson et al., col. 23, line 40 through col. 24, line 2). Robinson goes on to disclose the use of longer

wavelengths to activate the photosensitizer drug. See id. Thus, based on the teachings of Robinson, one skilled in the art would neither consider utilizing short wavelengths of light to activate the photosensitizer drug, nor appreciate the benefits of using short wavelengths for this purpose. Accordingly, the method according to claims 1-59 are patentably distinguishable from the method disclosed in Robinson and not obvious in view of Robinson. Therefore, reconsideration and withdrawal of the rejection based upon this reference are respectfully urged.

III. Lamuraglia Does Not Teach the Claimed Invention.

The Examiner rejected claims 1-57 (claim 56 has been cancelled) under 35 U.S.C. § 103(a) as being unpatentable over Lamuraglia. (WO 01/24825 A2). Lamuraglia generally describes a method of PDT treatment using wavelengths of light longer than 610 nm. Specifically, Lamuraglia teaches the use of 660 nm and 690 nm wavelengths. Contrary to the Lamuraglia reference, the present invention utilizes wavelengths of light in the 390 to 610 nm range to simultaneously achieve safety and efficacy. Accordingly, the method according to claims 1-57 is patentably distinguishable from the method disclosed in Lamuraglia and furthermore, based on the teaches of Lamuraglia, one skilled in the art would neither consider utilizing short wavelengths of light to excite a photosensitizer drug, nor appreciate the benefits of using short wavelengths for this purpose. Therefore, reconsideration and withdrawal of the rejection based on this reference are respectfully urged.

IV. The Invention of the Subject Application was Conceived and Diligently Reduced to Practice Prior to the Earliest Effective Date of the Allison Reference.

With respect to the rejection of claims 1-57 (claim 56 has been cancelled) the Examiner also cites Allison (WO 01/35997 A2) in support of the Examiner's position. The Allison reference indicates that it was published on May 25, 2001. As demonstrated by the Rule 131 Affidavit attached hereto as Exhibit A, the subject invention was conceived prior to May 25, 2001, the earliest effective date of the Allison reference. (See Exh. A). Thereafter, the inventor worked diligently on reducing the invention to practice at least through and until the filing of the above-caption application. (See Exh. A). Accordingly the Allison reference is antedated and does not bar the grant of a patent on the subject application.

V. Conclusion.

Accordingly, it is respectfully requested that the Examiner allow claims 1-60. The Examiner is encouraged to contact the undersigned attorney by telephone to resolve any remaining issues.

Respectfully submitted,

By: _____

Roxana Wizorek
Registration No. 46,110
BRYAN CAVE LLP
211 North Broadway, Ste. 3600
St. Louis, MO 63102
Tele. (314) 259-2699
Facs. (314) 259-2020

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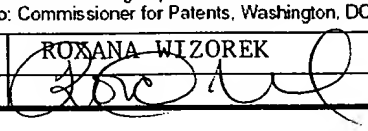
Signature		Date	03/04/2003

APPENDIX A

Pursuant to 37 CFR 1.121 (b)(iii) the following are versions of the replacement paragraphs marked up (by brackets for deleted matter and underlining for added matter) to show changes.

A. Paragraph at page 4, line 20 through page 5, line 8:

> Other studies have investigated the inhibition of neointima formation in natural vein grafts in which, prior to implantation, the graft receives a PDT treatment using 675 nm light (G. M. LaMuraglia, et al., Photodynamic Therapy of Vein Grafts: Suppression of Intimal Hyperplasia of the Vein Graft but not the Anastomosis, J Vascular Surg, 21, 1995). Still further studies have investigated the reduction or stabilization of plaques in diseased artery animal models using a photosensitizer delivered systemically and excited with either external or intravascular light with a wavelength near 730 nm. These studies led to the application of PDT in human clinical trials using Lutetium [texaphryn] <u>texaphyrin</u> (LuTex) in combination with a laser source having a wavelength near 730 nm (S. G. Rockson, et al., Photoangioplasty: An Emerging Clinical Cardiovascular Role for Photodynamic Therapy, Circulation, 102, 591-96, 2000). These human clinical trials have two primary efficacy endpoints: inhibition of restenosis following angioplasty based interventions and reduction/stabilization of plaques in atherosclerotic lesions.

B. Paragraph at page 6, line 12 through page 6, line 21:

> A third factor that has led researchers to rely on wavelengths greater than 630 nm is based on the geometric falloff of light emitted from a cylindrical or point source. As light radiates outward from either a cylindrical source or a point source, it must decrease in intensity since it is gradually spread over an ever-increasing volume. This conclusion is a result of basic physics and is [a] simply a consequence of the law of conservation of energy. Furthermore, even in the red/infrared portion of the spectrum, light undergoes relatively strong absorption and scattering by tissue. Therefore, in addition to the geometric falloff, both absorption and scattering limit the penetration depth of light into surrounding tissues, even in the red/infrared portion of the spectrum. The combination of this, along with the previously mentioned factors, has led to the exclusive use of wavelengths of 630 nm and greater in cardiovascular PDT studies to date.

C. Paragraph at page 7, line 18 through page 8, line 14:

> We have discovered that photosensitizer selectivity alone is insufficient to ensure minimal damage to surrounding tissue while simultaneously

providing the desired level of efficacy within the targeted cardiovascular tissue. A wide variety of tissue types, such as myocardium, lung, nerves, adjacent vessels, fat, etc. are typically located near target vessels. In practice, it is nearly impossible for a drug to have the necessary preferential uptake characteristics in the target tissue, while not being taken up to some degree in these surrounding tissues as well. We have found that in situations where such surrounding tissues contain some amount of the photosensitizer [present], there is an especially difficult challenge in the practical implementation of PDT using red/infrared light. Penetration of light in this wavelength range appears to cause undesired PDT treatment in important underlying tissues that are well beyond the desired treatment zone of the [artery] vessel, thereby making it difficult to control treatment depth. Furthermore, while in theory it might be possible to accurately control the treatment depth by delivery of a specific light dose at the surface of the vessel lumen, this may be difficult to achieve in practice, due to the variations in tissue optical properties as well as the difficulty in accurately controlling the light level at all surfaces when using intravascular light. Furthermore, drug uptake will vary within the target treatment zone (even for the same tissue type) and the optical properties of the target tissue will vary between patients. These various factors will lead to significant practical limitations associated with variations in treatment depth, especially for wavelengths of 630 nm and greater. In practice, some regions in the target treatment area will receive an insufficient depth of treatment while others well outside the target treatment area will incur detrimental PDT effects.

D. Paragraph at page 8, line15 through page 8, line 17:

> Accordingly, there is a continuing need for a cardiovascular PDT treatment that delivers light to sufficiently penetrate into the [blood] target tissue, while simultaneously preventing the light from significantly penetrating through the tissue surrounding the target area.

E. Paragraph at page 8, line 19 through page 10, line 6:

> The present invention involves excitation of photosensitizer drugs for treatment of cardiovascular occlusions using wavelengths selected to improve efficacy and safety over previous approaches. Through the use of wavelengths in the 390-610 nm range, there is minimal surrounding tissue damage and simultaneously a very significant PDT effect is achieved within the vessel which is the target of the treatment. Selection of the particular range of wavelengths is based on the scattering properties of tissue and the detailed absorption spectrum of hemoglobin and the critical role they play in light penetration in tissue. Absorption and scattering preferably prevents light from penetrating as deeply as with wavelengths in the red/infrared portion of the spectrum. In particular, at wavelengths in

the 390-610 nm region, the optical penetration depth is comparable to the desired depth of treatment in cardiovascular applications of PDT. This in turn provides a means to eliminate many of the disadvantages that have been identified above for red or infrared light. Within the spectral region of 390-610 nm, the region of 440-610 nm is preferred when using devices that provide less efficient blood elimination or when a deeper depth of treatment is desired. This more restricted range is based on the fact that these wavelengths are on the long wavelength side of the Soret band for hemoglobin, thus there is not the severe attenuation by blood that exists for the shorter wavelengths. This method thereby allows sufficient penetration to treat thicker vessels to the desired depth in a reasonable time. This technique is applicable to all photosensitizers with sufficient absorption in this wavelength region. Here, sufficient absorption means an absorption coefficient high enough to allow treatment within a clinically relevant time period using available laser sources and allowable drug doses. This invention applies to, but is not limited to, photosensitizers of the following classes: texaphyrins, benzoporphyrin derivatives (including [Bisudyne] Visudyne), azaporphyrins, phthalocyanines, purpurins, Rose Bengal, xanthenes, porphycyanines, isomeric porphyrins, pentaphyrins, sapphyrins, phlorins, benzochlorins, hypericins, anthraquinones, rhodanols, barbituric acid [dyes] derivatives, expanded porphyrins, dipyrromethenes, coumarins, azo dyes, acridines, rhodanine[s] dyes, azine [dyes] derivatives, tetrazolium derivatives [dyes], safranines, indocyanines, indigo derivatives, indigo [dyes,] triazine derivatives [dyes], pyrrole derived macrocyclic compounds, naturally occurring or synthetic porphyrins, naturally occurring or synthetic chlorines, naturally occurring or synthetic bacteriochlorins, naturally occurring or synthetic isobacteriochlorins, naphthalocyanines, phenoxazine derivatives, phenothiazine[s] derivatives, chaloorganapyrylium derivatives, triarylmethane derivatives, rhodamine[s] derivatives, fluorescein derivatives, [and] verdin derivatives, toluidine blue derivatives, methylene blue derivatives, methylene violet derivatives, nile blue derivatives, nile red derivatives, phenazine derivatives, pinacyanol derivatives, plasmocorinth derivatives and indigo derivatives (included in this list is any combination of these photosensitizers as well as these photosensitizers in combination with other chemical substances).

F. Paragraph at page 11, lines 5-6:

Figure 5 is an image of a porcine heart harvested at 3 days after receiving PDT in a coronary artery using MV6401 and intravascular red light (approximately 664 nm);

G. Paragraph at page 11, lines 7-8:

Figure 6 is an image of a porcine heart harvested at 3 days after receiving PDT in a coronary artery using MV6401 and intravascular blue light (approximately 458 nm);

H. Paragraph at page 11, lines 9-10:

Figure 7 is an image of a porcine heart harvested at 3 days after receiving PDT in a coronary artery using MV6401 and intravascular green light (approximately 532 nm);

I. Paragraph at page 12, line 12 through page 13, line 23:

The present invention provides a method for PDT treatment to inhibit, stabilize or reduce occlusions in the cardiovascular system by exciting photosensitizer drugs using intravascular light at a wavelength in the range of 390-610 nm. While investigators in the PDT field have consistently pointed out the advantages of using red/infrared light excitation, our results, while inconsistent with those viewpoints and unexpected, indicate that alternative wavelengths which are less penetrating will provide an improved method of treatment. The previous approach of using red/infrared wavelengths was based in part on taking advantage of the fact that the attenuation of light by tissue and blood reaches a minimum in the red/infrared part of the spectrum. However, we have discovered that, in direct contrast to this view, wavelengths outside this red/infrared spectral region are optimal for PDT-based cardiovascular treatments. While in theory, wavelengths in the mid-infrared could be used, we have found that the most effective wavelengths are those coincident with spectral regions of significant absorption by hemoglobin, in particular, wavelengths in the 390-610 nm range. This choice of wavelength range is based on the objective of providing a practical, safe and effective PDT treatment. Wavelengths less than 390 nm are in the ultraviolet portion of the spectrum. Such wavelengths have several drawbacks including absorption by other chromophores within tissue, potential for mutagenicity, lack of convenient light sources and tendency to cause light-induced damage of optical components. In the case of 610 nm, this wavelength corresponds to the onset of strong absorption by hemoglobin in blood, as hemoglobin has a relatively strong absorption for light having wavelengths less than approximately 610 nm. Therefore, by using excitation sources having wavelengths of 610 nm or shorter, one may take advantage of hemoglobin absorption to limit the PDT treatment to the target treatment zone. This approach appears to limit the degree of surrounding tissue damage to an acceptable level and simultaneously provides a significant PDT treatment in the target tissue, which was not practical with the approach of the prior art. Furthermore, to be effective, the preferred method uses this concept with photosensitizers having relatively strong absorption (greater than 1000 L cm^{-1} M^{-1}). Photosensitizers having absorption coefficients less than this cannot be efficiently excited, resulting in the need to use high

light irradiances, high light doses or high drug doses. High light irradiances can lead to thermal injury while high light doses require long treatment times and high drug doses raise the prospect of drug related toxicities. An advantage of PDT photosensitizers over other photoactive molecules, such as psoralens, is their absorption spectra. Specifically, PDT photosensitizers typically have relatively strong absorption features within this ideal spectral range that allow them to be efficiently excited using wavelengths within the range of 390-610 nm. Furthermore, PDT photosensitizers are not believed to significantly penetrate the cell nucleus, thereby avoiding any questions of treatment related mutagenic effects as have been raised with alternative therapies[, such as psoralen based therapies].

J. Paragraph at page 15, line 17 through page 16, line 2:

This invention may require removal of blood from the region between the light delivery device and the target tissue. For devices in which a limited amount of blood remains in this region or for which moderately deep treatment is desired, excitation in approximately the 440-610 nm range is preferred due to the relatively [lower] higher absorption by blood than occurs at shorter wavelengths. Specifically, wavelengths of approximately 440 nm and greater are on the long wavelength side of the Soret band for hemoglobin, such that for these wavelengths there is not the severe attenuation by blood that exists at shorter wavelengths. On the other hand, for devices that provide very efficient removal of blood, all wavelengths in the 390-610 nm range are effective.

K. Paragraph at page 16, lines 3-20:

This technique is applicable to all photosensitizers with sufficient absorption in this wavelength region. Here, sufficient absorption means an absorption coefficient high enough to allow treatment within a clinically relevant time period using available laser sources and allowable drug doses. The preferred value of the molar extinction coefficient at the treatment wavelength is about 1000 L cm^{-1} M^{-1} or greater. Compounds meeting these criteria include, but [is] are not limited to, the following list of chemical classes, their derivatives and combinations of these: texaphyrins, benzoporphyrin derivatives (including Visudyne), azaporphyrins, phthalocyanines, purpurins, Rose Bengal, xanthenes, porphycyanines, isomeric porphyrins, pentaphyrins, sapphyrins, phlorins, benzochlorins, hypericins, anthraquinones, rhodanols, barbituric acid [dyes] derivatives, expanded porphyrins, dipyrromethenes, coumarins, azo dyes, acridines, rhodanines [dyes], azine [dyes] derivatives, tetrazolium [dyes] derivatives, safranines, indocyanines, indigo dyes, triazine [dyes] derivatives, pyrrole derived macrocyclic compounds, naturally occurring or synthetic porphyrins, naturally occurring or synthetic chlorines,

naturally occurring or synthetic bacteriochlorins, naturally occurring or synthetic isobacteriochlorins, naphthalocyanines, phenoxazine derivatives, phenothiazine[s] derivatives, chaloorganapyrylium derivatives, triarylmethane derivatives, rhodamine[s] derivatives, fluorescein derivatives, [and] verdin derivatives, toluidine blue derivatives, methylene blue derivatives, methylene violet derivatives, nile blue derivatives, nile red derivatives, phenazine derivatives, pinacyanol derivatives, plasmocorinth derivatives and indigo derivatives.

APPENDIX B

Pursuant to 37 CFR 1.121 (c)(1)(ii) the following are versions of the replacement claims marked up (by brackets for deleted matter and underlining for added matter) to show changes

2. The method of claim 1 wherein the photosensitizer drug is [a texaphryn] texaphyrin or a derivative thereof.

3. The method of claim 2 wherein the photosensitizer drug is lutetium [texaphryn] texaphyrin.

5. The method of claim 1 wherein the photosensitizer drug is a benzoporphyrin or a derivative thereof.

7. The method of claim 5 wherein the photosensitizer drug is [Bisudyne] Visudyne.

8. The method of claim 1 wherein the photosensitizer drug is a xanthene or a derivative thereof.

10. The method of claim 1 wherein the photosensitizer drug is [azoporphyrin] azaporphyrin or a derivative thereof.

11. The method of claim 1 wherein the photosensitizer drug is a phthalocyanine or a derivative thereof.

13 The method of claim 1 wherein the photosensitizer drug is [pupurin] a purpurin or a derivative thereof.

15. The method of claim 1 wherein the photosensitizer drug is a porphycyanine or a derivative thereof.

16. The method of claim 1 wherein the photosensitizer drug is an isomeric porphyrin or a derivative thereof.

17. The method of claim 1 wherein the photosensitizer drug is a pentaphyrin or a derivative thereof.

18. The method of claim 1 wherein the photosensitizer drug is a sapphyrin or a derivative thereof.

19. The method of claim 1 wherein the photosensitizer drug is a phlorin or a derivative thereof.

21. The method of claim 1 wherein the photosensitizer drug is a benzochlorin or a derivative thereof.

22. The method of claim 1 wherein the photosensitizer drug is a hypericin or a derivative thereof.

23. The method of claim 1 wherein the photosensitizer drug is an anthraquinone or a derivative thereof.

24. The method of claim 1 wherein the photosensitizer drug is a rhodanol or a derivative thereof.

25. The method of claim 1 wherein the photosensitizer drug is a barbituric acid [dye] or a derivative thereof.

27. The method of claim 1 wherein the photosensitizer drug is a dipyrromethene or a derivative thereof.

28. The method of claim 1 wherein the photosensitizer drug is a coumarin or a derivative thereof.

29. The method of claim 1 wherein the photosensitizer drug is an azo [dye] or a derivative thereof.

30. The method of claim 1 wherein the photosensitizer drug is an acridine or a derivative thereof.

31. The method of claim 1 wherein the photosensitizer drug is a rhodanine [dye] or a derivative thereof.

32. The method of claim 1 wherein the photosensitizer drug is an azine [dye] or a derivative thereof.

33. The method of claim1 wherein the photosensitizer drug is a tetrazolium [dye] or a derivative thereof.

34. The method of claim 1 wherein the photosensitizer drug is a safranine or a derivative thereof.

35. The method of claim 1 wherein the photosensitizer drug is an indocyanine or a derivative thereof.

36. The method of claim 1 wherein the photosensitizer drug is an indigo dye or a derivative thereof.

37. The method of claim 1 wherein the photosensitizer drug is a triazine [dye] or a derivative thereof.

38. The method of claim 1 wherein the photosensitizer drug is a pyrrole derived macrocyclic compound or a derivative thereof.

39. The method of claim 1 wherein the photosensitizer drug is a naturally occurring or synthetic isobacteriochlorin or a derivative thereof.

40. The method of claim 1 wherein the photosensitizer drug is a naphthalocyanine or a derivative thereof.

41. The method of claim 1 wherein the photosensitizer drug is a phenoxazine or a derivative thereof.

42. The method of claim 1 wherein the photosensitizer drug is a phenothiazine or a derivative thereof.

43. The method of claim 1 wherein the photosensitizer drug is a chaloorganapyrylium or a derivative thereof.

44. The method of claim 1 wherein the photosensitizer drug is a triarylmethane or a derivative thereof.

45. The method of claim 1 wherein the photosensitizer drug is a rhodamine or a derivative thereof.

47. The method of claim 1 wherein the photosensitizer drug is a verdin or a derivative thereof.

48. The method of claim 1 wherein the photosensitizer drug is touidine blue [dye] or a derivative thereof.

49. The method of claim 1 wherein the photosensitizer drug is methylene blue [dye] or a derivative thereof.

51. The method of claim 1 wherein the photosensitizer drug is nile blue [dye] or a derivative thereof.

53. The method of claim 1 wherein the photosensitizer drug is a phenazine or a derivative thereof.

54. The method of claim 1 wherein the photosensitizer drug is a pinacyanol or a derivative thereof.